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Set     Items   Description
S1        124   ((TSP OR THROMBOSPONDIN)(W)(2 OR II))(S)(ANTICANCER? OR CA-
                NCER? OR ANTICARCINOM? OR CARCINOM? OR ANTITUMOR OR TUMOR? OR
                ANTINEOPLAS OR NEOPLAS? OR MALIG? OR SKIN OR EPIDERM? OR DERM-
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S2         43   RD (unique items)
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 2/AB/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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13136009   BIOSIS NO.: 200100343158
 Thrombospondin-2 plays a protective role in multistep carcinogenesis: A
 novel host anti- tumor defense mechanism.
AUTHOR: Hawighorst Thomas; Velasco Paula; Streit Michael; Hong Young-Kwon;
  Kyriakides Themis R; Brown Lawrence F; Bornstein Paul; Detmar Michael(a)
AUTHOR ADDRESS: (a)Cutaneous Biology Research Center and Department of
  Dermatology, Massachusetts General Hospital and Harvard Medical School,
  Charlestown, MA, 02129: michael.detmar@cbrc2.mgh.harvard.edu**USA
JOURNAL: EMBO (European Molecular Biology Organization) Journal  20 (11):p
2631-2640 June 1, 2001
MEDIUM: print
ISSN: 0261-4189
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The angiogenic switch during tumorigenesis is thought to be
  induced by a change in the balance of pro-angiogenic and anti-angiogenic
  factors. To elucidate the biological role of the endogenous angiogenesis
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inhibitor thrombospondin -2 (TSP -2) during multistep carcinogenesis, we subjected TSP -2 -deficient and wild-type mice to a chemical skin carcinogenesis regimen. Surprisingly, TSP -2 expression was strongly upregulated in the mesenchymal stroma of wild-type mice throughout the consecutive stages of tumorigenesis whereas the angiogenesis factor, vascular endothelial growth factor, was induced predominantly in tumor cells. TSP -2 deficiency dramatically enhanced susceptibility to skin carcinogenesis and resulted in accelerated and increased tumor formation. The angiogenic switch occurred in early stages of pre-malignant tumor formation, and tumor angiogenesis was significantly enhanced in TSP -2 -deficient mice. While TSP -2 deficiency did not affect tumor differentiation or proliferation, tumor cell apoptosis was significantly reduced. These results reveal upregulation of an endogenous angiogenesis inhibitor during multistep tumorigenesis and identify enhanced stromal TSP -2 expression as a novel host anti-tumor defense mechanism.

2001

2/AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13031340 BIOSIS NO.: 200100238489
Extracellular matrix metalloproteinase 2 levels are regulated by the low density lipoprotein-related scavenger receptor and thrombospondin 2.
AUTHOR: Yang Zhantao; Strickland Dudley K; Bornstein Paul(a)
AUTHOR ADDRESS: (a)Dept. of Biochemistry, University of Washington, Seattle, WA, 98195: bornsten@u.washington.edu**USA
JOURNAL: Journal of Biological Chemistry 276 (11):p8403-8408 March 16, 2001
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: We have recently shown that the adhesive defect observed in dermal fibroblasts derived from thrombospondin 2 (TSP2)-null mice-results from an increase in matrix metalloproteinase 2 (MMP2) levels (Yang, Z., Kyriakides, T. R., and Bornstein, P. (2000) Mol. Biol. Cell 11, 3353-3364). Adhesion was restored by replacement of TSP2 and by inhibitors of MMP2 activity. In pursuing the observation that TSP2 and MMP2 interact, we now demonstrate that this interaction is required for optimal clearance of extracellular MMP2 by fibroblasts. Since TSP2 is known to be endocytosed by the scavenger receptor, low density lipoprotein receptor-related protein (LRP), we determined whether interference with LRP function affected fibroblast adhesion and/or extracellular MMP2 levels. Addition of heparin, which competes for the binding of TSP2 to LRP coreceptor proteoglycans, inhibited adhesion of control but not TSP2-null cells, and a blocking antibody to LRP as well as the LRP inhibitor, receptor-associated protein, also inhibited adhesion and increased MMP2 levels only in control fibroblasts. TSP2 did not inhibit active MMP2 directly and did not inhibit the activation of pro-MMP2. Finally, the internalization of 125I-MMP2 was reduced in TSP2-null compared with control fibroblasts. We propose that clearance of MMP2-TSP2 complexes by LRP is an important mechanism for the regulation of extracellular MMP2 levels in fibroblasts, and perhaps in other cells. Thus, some features of the phenotype of TSP2-null mice, such as abnormal collagen fibrillogenesis, accelerated wound healing, and increased

angiogenesis, could result in part from increased MMP2 activity.

2001

2/AB/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12919659 BIOSIS NO.: 200100126808
Matricellular proteins as modulators of cell-matrix interactions: Adhesive defect in thrombospondin 2-null fibroblasts is a consequence of increased levels of matrix metalloproteinase-2.
AUTHOR: Yang Zhantao; Kyriakides Themis R; Bornstein Paul(a)
AUTHOR ADDRESS: (a)Department of Biochemistry, University of Washington, Seattle, WA, 98195: bornsten@u.washington.edu**USA
JOURNAL: Molecular Biology of the Cell 11 (10):p3353-3364 October, 2000
MEDIUM: print
ISSN: 1059-1524
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Thrombospondin 2 (TSP2)-null mice, generated by disruption of the Thbs2 gene, display a variety of connective tissue abnormalities, including fragile skin and the presence of abnormally large collagen fibrils with irregular contours in skin and tendon. In this study we demonstrate that TSP2-null skin fibroblasts show a defect in attachment to a number of matrix proteins, and a reduction in cell spreading. To investigate the molecular mechanisms responsible for these abnormal cell-matrix interactions, we compared the levels of matrix metalloproteinases (MMPs) in wild-type and mutant fibroblasts. Isolation and analysis of gelatinases from conditioned media by gelatin-agarose affinity chromatography and gelatinolytic assays demonstrated that TSP2-null fibroblasts produce a 2-fold increase in gelatinase A (MMP2) compared with wild-type cells. The adhesive defect was corrected by treatment of TSP2-null fibroblasts with soluble TSP2, with the MMP inhibitors BB94 and tissue inhibitor of metalloproteinase-2, and with a neutralizing antibody to MMP2. Moreover, stable transfection of TSP2-null fibroblasts with mouse TSP2 cDNA corrected both the adhesive defect and the altered expression of MMP2. Finally, MMP2 was shown to interact with TSP2 in a direct-binding plate assay. We conclude that TSP2 plays an important role in cell-matrix interactions, and that a deficiency in the protein results in increased levels of MMP2 that contribute to the adhesive defect in TSP2-null fibroblasts and could play a role in the complex phenotype of TSP2-null mice.

2000

2/AB/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12893598 BIOSIS NO.: 200100100747
Gene expression of angiogenesis related factors in glioma.
AUTHOR: Osada Hideo; Tokunaga Tetsuji; Hatanaka Hiroyuki; Kawakami Tsutomu; Tsuchida Takashi; Abe Yoshiyuki; Tsugu Atsushi; Kijima Hiroshi; Yamazaki Hitoshi; Shima Katsuji; Osamura Yoshiyuki; Ueyama Yoshito; Nakamura Masato(a)
AUTHOR ADDRESS: (a)Department of Pathology, Tokai University School of

Medicine, Bohseidai, Isehara, Kanagawa, 259-1193:
mnakamur@is.icc.u-tokai.ac.jp**Japan
JOURNAL: International Journal of Oncology 18 (2):p305-309 February, 2001
MEDIUM: print
ISSN: 1019-6439
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Angiogenesis plays an important role in growth and proliferation of cancer. Various angiogenic and angiostatic factors regulate angiogenesis. In this study, we examined gene expression of the angiopoietin family including angiopoietin 1 (Ang1) and angiopoietin 2 (Ang2) in 39 gliomas and 5 glioma-xenografts by RT-PCR. Ang1 and Ang2 genes were expressed in 54%, and 77% of gliomas, respectively. The expression of Ang1 was significantly correlated with the expression of Ang2. Both Ang1 and Ang2 were shown to be expressed in the glioma cells. Ang2 gene expression was correlated with VEGF gene expression. Angiopoietin molecules may synergistically cooperate in growth and vascularization in glioma.

2001

2/AB/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12888697 BIOSIS NO.: 200100095846
Comparative study of angiostatic and anti-invasive gene expressions as prognostic factors in gastric cancer.
AUTHOR: Lee Ji Hee; Koh Jeong Tae; Shin Boo Ahn; Ahn Kyu Youn; Roh Jung Ho; Kim Young Jin; Kim Kyung Keun(a)
AUTHOR ADDRESS: (a)Department of Pharmacology, College of Dentistry, Chonnam National University, Hak-Dong 5, Dong-Ku, Kwangju, 501-190: kimkk@chonnam.chonnam.ac.kr**South Korea
JOURNAL: International Journal of Oncology 18 (2):p355-361 February, 2001
MEDIUM: print
ISSN: 1019-6439
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Genes involving angiogenesis and metastasis play an important role in the progression and infiltration of cancer . We examined the expressions of various angiostatic and potential invasion/metastasis suppressor genes through RT-PCR analyses in 32 gastric cancer specimens with or without distant metastasis. The expressions of the invasion/metastasis suppressor, nm23 and E-cadherin increased much more in the cancer tissue (CT) and metastatic lymph node (MLN) than in the extraneoplastic mucosa (EM) and non-metastatic lymph node (NLN), respectively. The expressions of the angiostatic factor, angiopoietin 2 and thrombospondin 2 increased in the CT and MLN as compared with the EM and NLN, respectively. The newly cloned angiostatic factor, brain-specific angiogenesis inhibitor 1 (BAI1) decreased much more in the CT and MLN than the EM and NLN, respectively. However, BAI1 increased in the CT compared with the EM among the patients with poor prognosis and distant metastasis, such as liver or peritoneum. The expressions of the invasive factor, matrix metalloproteinase-2 and its suppressor, tissue inhibitor metalloproteinase-2 (TIMP-2) increased in the CM as compared

with the EM, but the increased expression pattern of these genes in the CT became blunted among the patients with good prognosis. Our results indicate that BAI1 and TIMP-2 expressions in the extraneoplastic mucosa and non-metastatic lymph nodes were not suppressed in the patients with good prognosis, but increased expression of angiopoietin 2, thrombospondin 2 , TIMP-2, nm23 and E-cadherin in the tumor tissue did not lead to a long survival after operation. It is suggested that the extent of BAI1 and TIMP-2 expression in the gastric mucosa may be an important prognostic factor for predicting survival in gastric cancer . 2001

2/AB/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12878369 BIOSIS NO.: 200100085518
Thrombospondin-1 and -2 in node-negative breast cancer: Correlation with angiogenic factors, p53, cathepsin D, hormone receptors and prognosis.
AUTHOR: Gasparini Giampietro(a); Toi Masakazu; Biganzoli Elia; Dittadi Ruggero; Fanelli Massimo; Morabito Alessandro; Boracchi Patrizia; Gion Massimo
AUTHOR ADDRESS: (a)Division of Medical Oncology, Azienda Complesso Ospedaliero 'San Filippo Neri', Via Martinotti 20, I-00135, Rome**Italy
JOURNAL: Oncology (Basel) 60 (1):p72-80 December, 2001
MEDIUM: print
ISSN: 0030-2414
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Objective: Thrombospondins (TSPs) are a multigene family of five secreted glycoproteins involved in the regulation of cell proliferation, adhesion and migration. Two members of the TSP family, namely TSP-1 and TSP -2 , are also naturally occurring inhibitors of angiogenesis. The aim of the present study was to determine the prognostic significance of the determination of TSP-1 and -2 and their correlation with the angiogenic pepticles vascular endothelial growth factor (VEGF) and thymidine phosphorylase (TP), as well as with other biological and clinicopathological features investigated. Methods: We evaluated a series of 168 women with node-negative breast cancer with a median follow-up period of 66 months, not treated with adjuvant therapy. The cytosolic levels of TSP-1 and -2 were determined in the primary tumour by a commercially available immunometric assay. Results: We found that 166 tested tumours had measurable levels of TSP-1 and -2 protein (median value 5.978, range 0.579-31.410 ng/mg of protein). On the basis of Spearman's rank correlation coefficient, a weak inverse association of TSP-1 and -2 with tumour size and cathepsin D was found. Moreover, principal component analysis on ranks evidenced a poor association between TSP-1 and -2, VEGF and TP. The results of the clinical outcome were analysed by both univariate and multivariate (for relapse-free survival (RFS) only)) Cox regression models. TSP-1 and -2 were not significant prognostic factors in univariate analysis for either RFS ($p = 0.427$) or overall survival ($p = 0.069$). To investigate the 'angiogenic balance hypothesis', bivariate analyses were performed to investigate the interactions of TSP-1 and -2 with VEGF, TP or p53, but none were included in the selected models. Finally, in multivariate analysis for RFS a baseline model, previously defined in a larger case series and inclusive of VEGF, TP and their interaction was adopted. It was highly significant ($p = 0.002$, Harrell c statistic value of 0.703); but when TSP-1 and -2 were added, their contribution was negligible ($p = 0.731$, Harrell c

statistic value of 0.705). Conclusions: The results of this study suggest that TSP-1 and -2 do not provide additional prognostic contribution to the joint effects of VEGF and TP. In the series of node-negative breast cancer patients investigated, determination of the angiogenic peptides VEGF and TP gave significant prognostic information. On the contrary, TSP-1 and -2, potential naturally occurring negative regulators of angiogenesis, lacked of prognostic value.

2001

2/AB/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12872443 BIOSIS NO.: 200100079592
The role of VEGF and thrombospondins in skin angiogenesis.
AUTHOR: Detmar Michael(a)
AUTHOR ADDRESS: (a)Cutaneous Biology Research Center, Department of Dermatology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, 02129: michael.detmar@cbrc2.mgh.harvard.edu**USA
JOURNAL: Journal of Dermatological Science 24 (Suppl. 1):pS78-S84
December, 2000
MEDIUM: print
ISSN: 0923-1811
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The vasculature in adult skin remains normally quiescent, due to the dominant influence of endogenous angiogenesis inhibitors over angiogenic stimuli. However, skin retains the capacity for brisk initiation of angiogenesis, the growth of new blood vessels from preexisting vessels, during tissue repair and in numerous diseases, including inflammatory skin diseases such as psoriasis and skin cancers such as cutaneous squamous cell carcinomas. Moreover, cyclic vascular expansion occurs during the growth phase of the hair follicle. Recent evidence suggests vascular endothelial growth factor as the major skin angiogenesis factor. During skin angiogenesis, expression of vascular endothelial growth factor is induced in epidermal keratinocytes by several stimuli including transforming growth factor-alpha and hypoxia, leading to increased vascularization of the dermis. In contrast, vascular endothelial growth factor-C induces skin lymphangiogenesis. Thrombospondin-1 and thrombospondin -2 are endogenous inhibitors of angiogenesis that are expressed in normal skin , maintaining the quiescence of cutaneous vessels. Both inhibitors potently inhibit skin cancer growth via inhibition of tumor angiogenesis. Targeting cutaneous blood vessels represents a promising new therapeutic approach for the treatment of a variety of skin diseases.

2000

2/AB/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12841790 BIOSIS NO.: 200100048939
Thrombospondin 2, a matricellular protein with diverse functions.
AUTHOR: Bornstein Paul(a); Armstrong Lucas C; Hankenson Kurt D; Kyriakides Themis R; Yang Zhantao

AUTHOR ADDRESS: (a)Department of Biochemistry, University of Washington, Seattle, WA, 98195: bornsten@u.washington.edu**USA
JOURNAL: Matrix Biology 19 (7):p557-568 December, 2000
MEDIUM: print
ISSN: 0945-053X
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Thrombospondin (TSP) 2 is a close relative of TSP1 but differs in its temporal and spatial distribution in the mouse. This difference in expression undoubtedly reflects the marked disparity in the DNA sequences of the promoters in the genes encoding the two proteins. The synthesis of TSP2 occurs primarily in connective tissues of the developing and growing mouse. In the adult animal the protein is again produced in response to tissue injury and in association with the growth of tumors . Despite the abnormalities in collagen fibrillogenesis, fragility of skin , and laxity of tendons and ligaments observed in the TSP2-null mouse, TSP2 does not appear to contribute directly to the structural integrity of connective tissue elements. Instead, emerging evidence supports a mode of action of TSP2 'at a distance', i.e. by modulating the activity and bioavailability of proteases and growth factors in the pericellular environment and, very likely, by interaction with cell-surface receptors. Thus, TSP2 qualifies as a matricellular protein, as defined in the introduction to this minireview series. The phenotype of TSP2-null mice has been very helpful in providing clues to the functions of TSP2. In addition to histological and functional abnormalities in connective tissues, these mice display an increased vascularity of the dermis and subdermal tissues, increased endosteal bone growth, a bleeding defect, and a marked adhesive defect of dermal fibroblasts. Our laboratory has established that TSP2 binds matrix metalloproteinase 2 (MMP2) and that the adhesive defect in TSP2-null fibroblasts results from increased MMP2 activity. The investigation of the basis for the other defects in the TSP2-null mouse is likely to yield equally interesting results.

2000

2/AB/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12554800 BIOSIS NO.: 200000308302
Tissue factor expression and angiogenesis in human prostate carcinoma.
AUTHOR: Abdulkadir Sarki A; Carvalhal Gustavo F; Kaleem Zaheed; Kisiel Walter; Humphrey Peter A; Catalona William J; Milbrandt Jeffrey
AUTHOR ADDRESS: (a)Washington University School of Medicine, 660 S Euclid Ave, St Louis, MO, 63110**USA
JOURNAL: Human Pathology 31 (4):p443-447 April, 2000
MEDIUM: print
ISSN: 0046-8177
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: In tumors , the switch to the angiogenic phenotype is thought to be controlled by a balance of positive and negative angiogenic factors. Tissue factor (TF) produced by tumor cells has been implicated in the regulation of this "angiogenic switch" through its ability to

concurrently induce the expression of angiogenic molecules such as vascular endothelial cell growth factor (VEGF), while inhibiting the expression of anti-angiogenic molecules such as thrombospondin 2 . We have examined TF expression and its relationship to angiogenesis and tumor progression in human prostate carcinomas . Most of the prostate carcinoma specimens examined (73%; n = 67) express high levels of TF. Immunohistochemical analysis localized TF expression to the epithelial cells of malignant glands. TF expression was significantly correlated with tumor angiogenesis as measured by the microvessel density (MVD). In addition, TF expression was correlated with the preoperative PSA level, a strong predictor of recurrence in prostate carcinomas . Our findings show that TF expression by the malignant glands in prostate cancer is common and suggest a role for this molecule in regulating prostate cancer progression and angiogenesis.

2000

2/AB/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12474943 BIOSIS NO.: 200000228445
Accelerated skin carcinogenesis in mice deficient in thrombospondin- 2 .
AUTHOR: Hawighorst T(a); Velasco P(a); Streit M(a); Bornstein P; Detmar M (a)
AUTHOR ADDRESS: (a)Cutaneous Biology Research Center, Department of Dermatology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA**USA
JOURNAL: Journal of Investigative Dermatology 114 (4):p762 April, 2000
CONFERENCE/MEETING: 61st Annual Meeting of the Society for Investigative Dermatology. Chicago, Illinois, USA May 10-14, 2000
ISSN: 0022-202X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

2/AB/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12471596 BIOSIS NO.: 200000225098
Thrombospondin- 2 is a novel endogenous inhibitor of tumor growth and angiogenesis.
AUTHOR: Streit M R W(a); Riccardi L(a); Velasco P(a); Brown L F; Hawighorst T(a); Bornstein P; Detmar M(a)
AUTHOR ADDRESS: (a)Massachusetts General Hospital, Charlestown, MA**USA
JOURNAL: Journal of Investigative Dermatology 114 (4):p751 April, 2000
CONFERENCE/MEETING: 61st Annual Meeting of the Society for Investigative Dermatology. Chicago, Illinois, USA May 10-14, 2000
ISSN: 0022-202X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

2/AB/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12471544 BIOSIS NO.: 200000225046
Identification of thrombospondin- 2 as a novel endogenous inhibitor of tumor growth and angiogenesis.
AUTHOR: Streit Michael(a); Riccardi L; Velasco P; Brown L F; Hawighorst T; Bornstein P; Detmar M
AUTHOR ADDRESS: (a)Harvard Med Sch, Boston, MA**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting (41):p489-490 March, 2000
CONFERENCE/MEETING: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

2/AB/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12463609 BIOSIS NO.: 200000217111
Increased and persistent inflammation and angiogenesis in delayed-type hypersensitivity reactions elicited in the skin of thrombospondin- 2 deficient mice.
AUTHOR: Lange-Asschenfeldt B(a); Velasco P(a); Bornstein P; Detmar M(a)
AUTHOR ADDRESS: (a)Massachusetts General Hospital, Charlestown, MA**USA
JOURNAL: Journal of Investigative Dermatology 114 (4):p757 April, 2000
CONFERENCE/MEETING: 61st Annual Meeting of the Society for Investigative Dermatology. Chicago, Illinois, USA May 10-14, 2000
ISSN: 0022-202X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

2/AB/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12340926 BIOSIS NO.: 200000094428
Thrombospondin- 2: A potent endogenous inhibitor of tumor growth and angiogenesis.
AUTHOR: Streit Michael; Riccardi Lucia; Velasco Paula; Brown Lawrence F; Hawighorst Thomas; Bornstein Paul; Detmar Michael(a)
AUTHOR ADDRESS: (a)Cutaneous Biology Research Center and Department of Dermatology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, 02129**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 96 (26):p14888-14893 Dec. 21, 1999
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Recent evidence suggests a potential role for thrombospondin -2 (TSP -2), a matricellular glycoprotein, in the regulation of primary angiogenesis. To directly examine the biological effect of TSP -2

expression on tumor growth and angiogenesis, human A431 squamous cell carcinoma cells, which do not express TSP -2 , were stably transfected with a murine TSP -2 expression vector or with vector alone. A431 cells expressing TSP -2 did not show an altered growth rate, colony-forming ability, or susceptibility to induction of apoptosis in vitro. However, injection of TSP -2 -transfected clones into the dermis of nude mice resulted in pronounced inhibition of tumor growth that was significantly stronger than the inhibition observed in A431 clones stably transfected with a thrombospondin-1 (TSP-1) expression vector, and combined overexpression of TSP-1 and TSP -2 completely prevented tumor formation. Extensive areas of necrosis were observed in TSP -2 -expressing tumors , and both the density and the size of tumor vessels were significantly reduced, although tumor cell expression of the major tumor angiogenesis factor, vascular endothelial growth factor, was maintained at high levels. These findings establish TSP -2 as a potent endogenous inhibitor of tumor growth and angiogenesis.

1999

2/AB/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12301913 BIOSIS NO.: 200000059780
Expression of angiostatic factors in colorectal cancer.
AUTHOR: Yoshida Yukiko; Oshika Yoshiro; Fukushima Yoshitaka; Tokunaga Tetsuji; Hatanaka Hiroyuki; Kijima Hiroshi; Yamazaki Hitoshi; Ueyama Yoshito; Tamaoki Norikazu; Miura Soichiro; Nakamura Masato(a)
AUTHOR ADDRESS: (a)Department of Pathology, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa**Japan
JOURNAL: International Journal of Oncology 15 (6):p1221-1225 Dec., 1999
ISSN: 1019-6439
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Angiogenesis plays an important role in growth and proliferation of cancer. Various angiogenic and angiostatic factors regulate angiogenesis. We examined expression of genes encoding various angiostatic factors: thrombospondin 1 (TSP1), thrombospondin 2 (TSP2), brain-specific angiogenesis inhibitor 1 (BAI1) and angiopoietin 2 (AGP2) in 62 colorectal cancers and 40 samples of extraneoplastic colon mucosa. The expression of the angiostatic factors TSP2 and AGP2 were significantly increased in the cancerous mucosa as compared to these in extraneoplastic mucosa (chi2 test; $p<0.0001$, and Fisher's exact test; $p<0.0001$), while the increase in TSP1 expression was not significant. BAI1 expression was slightly decreased in the cancer tissue. These results suggested that specific types of angiostatic factors might have protective roles against cancer cell proliferation via dormancy due to hyponutrition caused by decreased vascularity.

1999

2/AB/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12291525 BIOSIS NO.: 200000049392

Accelerated wound healing in mice with a disruption of the thrombospondin 2 gene.
AUTHOR: Kyriakides Themis R; Tam Jessica W Y; Bornstein Paul(a)
AUTHOR ADDRESS: (a)Department of Biochemistry, University of Washington, Seattle, WA**USA
JOURNAL: Journal of Investigative Dermatology 113 (5):p782-787 Nov., 1999
ISSN: 0022-202X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Mice that lack the extracellular matrix protein thrombospondin 2 have, among several abnormalities, an increase in vascular density, abnormal collagen fibrils, and dermal fibroblasts that are defective in adhesion. These findings suggested that responses involving these processes, such as wound healing, might be altered. To investigate the healing process, excisional wounds were made with the aid of a biopsy punch. Such wounds, observed over a 14 d period, appeared to heal at an accelerated rate and with less scarring in thrombospondin 2 -null mice. Histologic analysis of thrombospondin 2 -null wound sites revealed the presence of an irregularly organized and highly vascularized granulation tissue. In addition, thrombospondin 2 -null wounds retained a higher total cellular content, than control wounds. No differences in wound re-epithelization rates were observed, but thrombospondin 2 -null epithelia formed rete pegs and were thicker than control epithelia. By immunohistochemistry, we detected elevated levels and an irregular deposition pattern for fibronectin in thrombospondin 2 -null wounds, observations that correlated with the abnormal collagen organization in the granulation tissue. Immunostaining for thrombospondin 2 in control wounds showed that the protein is present in both early and late wounds, in a scattered cell-associated pattern or widely distributed cell- and matrix-associated pattern, respectively. Our results suggest that thrombospondin 2 plays a crucial part in the organization and vascularization of the granulation tissue during healing, possibly by modulating fibroblast-matrix interactions in early wounds and regulating the extent of angiogenesis in late wounds.

1999

2/AB/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12058741 BIOSIS NO.: 199900339260
CD36 is expressed in human bone and osteoclastoma and mediates thrombospondin-2-stimulated resorption.
AUTHOR: Carron J A(a); Tooney P A; Mosher D F; Gallagher J A(a)
AUTHOR ADDRESS: (a)Human Bone Cell Research Group, Dept. Human Anatomy and Cell Biology, University of Liverpool, L**UK
JOURNAL: Calcified Tissue International 64 (SUPPL. 1):pS57 1999
CONFERENCE/MEETING: XXVIth European Symposium on Calcified Tissues Maastricht, Netherlands May 7-11, 1999
SPONSOR: European Calcified Tissue Society
ISSN: 0171-967X
RECORD TYPE: Citation
LANGUAGE: English
1999

2/AB/18 (Item 18 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

11983844 BIOSIS NO.: 199900264363
The endogenous angiogenesis inhibitor thrombospondin- 2 is expressed in basal keratinocytes of normal epidermis in vivo and in epidermal keratinocytes in vitro.
AUTHOR: Riccardi L(a); Streit M(a); Velasco P(a); Brown L; Lawler J; Detmar M(a)
AUTHOR ADDRESS: (a)Cutaneous Biology Research Center, Department of Dermatology, Massachusetts General Hospital and**USA
JOURNAL: Journal of Investigative Dermatology 112 (4):p560 April, 1999
CONFERENCE/MEETING: 60th Annual Meeting of the Society for Investigative Dermatology Chicago, Illinois, USA May 5-9, 1999
ISSN: 0022-202X
RECORD TYPE: Citation
LANGUAGE: English
1999

2/AB/19 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11938265 BIOSIS NO.: 199900184374
TSP I and TSP II mRNA expression in lung carcinoma: Relationship with p53 alterations, angiogenic growth factors and vascular density.
AUTHOR: Fontanini Gabriella; Boldrini Laura; Calcinai Alessandra; Bevilacqua Generoso; Basolo Fulvio
AUTHOR ADDRESS: Dep. Oncol.-Div. Pathol., Univ. Pisas, Pisa**Italy
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 40p70 March, 1999
CONFERENCE/MEETING: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1999

2/AB/20 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11933182 BIOSIS NO.: 199900179291
Correlation between thrombospondin 2 gene expression and vascularity in non-small cell lung cancer.
AUTHOR: Nakamura M(a); Oshika Y(a); Hatanaka H(a); Tokunaga T(a); Ozeki Y; Kijima H(a); Yamazaki H; Tamaoki N(a); Ueyama Y(a)
AUTHOR ADDRESS: (a)Dep. Pathol., Tokai Univ. Sch. Med., Kanagawa 259-1193** Japan
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 40p556 March, 1999
CONFERENCE/MEETING: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1999

2/AB/21 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11933181 BIOSIS NO.: 199900179290
Thrombospondin 2 gene expression is angiostatic and anti-metastasis factor of colon cancer.
AUTHOR: Kijima H; Tokunaga T; Oshika Y; Fukushima Y; Nakamura M; Tomil Y; Yamazaki H; Tamaoki N; Ueyama Y
AUTHOR ADDRESS: Dep. Pathol., Tokai Univ. Sch. Med., Kanagawa 259-1193** Japan
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 40p556 March, 1999
CONFERENCE/MEETING: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1999

2/AB/22 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11848740 BIOSIS NO.: 199900094849
Thrombospondin 2 expression is correlated with inhibition of angiogenesis and metastasis of colon cancer.
AUTHOR: Tokunaga T; Nakamura M(a); Oshika Y; Abe Y; Fukushima Y; Hatanaka H ; Sadahiro S; Kijima H; Tsuchida T; Yamazaki H; Tamaoki N; Ueyama Y
AUTHOR ADDRESS: (a)Dep. Pathol., Tokai Univ. Sch. Med., Bohseidai, Isehara, Kkanagawa 259-1193**Japan
JOURNAL: British Journal of Cancer 79 (2):p354-359 Jan., 1999
ISSN: 0007-0920
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Two subtypes of thrombospondin (TSP-1 and TSP -2) have inhibitory roles in angiogenesis in vitro, although the biological significance of these TSP isoforms has not been determined in vivo. We examined TSP-1 and TSP -2 gene expression by reverse transcription polymerase chain reaction (RT-PCR) analysis in 61 colon cancers . Thirty-eight of these 61 colon cancers were positive for TSP -2 expression and showed hepatic metastasis at a significantly lower incidence than those without TSP -2 expression (P = 0.02). TSP -2 expression was significantly associated with M0 stage in these colon cancers (P = 0.03), whereas TSP-1 expression showed no apparent correlation with these factors. The colon cancer patients with TSP -2 expression showed a significantly low frequency of liver metastasis correlated with the cell-associated isoform of vascular endothelial growth factor (VEGF-189) (P = 0.0006). Vascularity was estimated by CD34 staining, and TSP -2 (-)/VEGF-189(+) colon cancers showed significantly increased vessel counts and density in the stroma (P < 0.0001), TSP -2 (-)VEGF-189(+) colon cancer patients also showed significantly poorer prognosis compared with those with TSP -2 (+)/VEGF-189(-) (P = 0.0014). These results suggest that colon cancer metastasis is critically determined by angiogenesis resulting from the balance between the angioinhibitory factor TSP -2 and angiogenic factor VEGF-189.

1999

2/AB/23 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11646824 BIOSIS NO.: 199800428555
The distribution of the matricellular protein thrombospondin 2 in tissues of embryonic and adult mice.
AUTHOR: Kyriakides Themis R; Zhu Yu-Hong; Yang Zhantao; Bornstein Paul(a)
AUTHOR ADDRESS: (a)Dep. Biochem., Box 357350, Univ. Washington, Seattle, WA 98195**USA
JOURNAL: Journal of Histochemistry and Cytochemistry 46 (9):p1007-1015 Sept., 1998
ISSN: 0022-1554
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mice that lack the matricellular protein thrombospondin 2 (TSP2) develop a pleiotropic phenotype characterized by morphological changes in connective tissues, an increase in vascular density, and a propensity for bleeding. Furthermore, dermal cells derived from TSP2-null mice display adhesion defects, a finding that implicates TSP2 in cell-matrix interactions. To gain a better understanding of the participation of TSP2 in the development and maturation of the mouse, we examined its distribution in embryonic and adult tissues. Special attention was paid to the presence of TSP2 in collagen fibers, because collagen fibrils in the TSP2-null mouse appear to be irregular in size and contour by electron microscopy. Immunohistochemical analysis of Day 15 and Day 18 embryos revealed TSP2 in areas of chondrogenesis, osteogenesis, and vasculogenesis, and in dermal and other connective tissue-forming cells. Distinctly different patterns of deposition of TSP2 were observed in areas of developing cartilage and bone at Days 15 and 18 of embryonic development. A survey of adult tissues revealed TSP2 in dermal fibroblasts, articular chondrocytes, Purkinje cells in the cerebellum, Leydig cells in the testis, and in the adrenal cortex. Dermal fibroblasts were also shown to synthesize TSP2 in vitro. The distribution of TSP2 during development is in keeping with its participation in the formation of a variety of connective tissues. In adult tissues, TSP2 is located in the pericellular environment, where it can potentially influence the cell-matrix interactions associated with cell movement and tissue repair.

1998

2/AB/24 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11335406 BIOSIS NO.: 199800116738
Mice that lack thrombospondin 2 display connective tissue abnormalities that are associated with disordered collagen fibrillogenesis, an increased vascular density, and a bleeding diathesis.
AUTHOR: Kyriakides Themis R; Zhu Yu-Hong; Smith Lynne T; Bain Steven D; Yang Zhantao; Lin Ming T; Danielson Keith G; Iozzo Renato V; Lamarca Mary ; McKinney Cindy E; Ginns Edward I; Bornstein Paul(a)
AUTHOR ADDRESS: (a)Dep. Biochem., Box 357350, Univ. Washington, Seattle, WA 98195**USA

JOURNAL: Journal of Cell Biology 140 (2):p419-430 Jan. 26, 1998
ISSN: 0021-9525
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Thrombospondin (TSP) 2 , and its close relative TSP1, are extracellular proteins whose functions are complex, poorly understood, and controversial. In an attempt to determine the function of TSP2, we disrupted the Thbs2 gene by homologous recombination in embryonic stem cells, and generated TSP2-null mice by blastocyst injection and appropriate breeding of mutant animals. Thbs2-/- mice were produced with the expected Mendelian frequency, appeared overtly normal, and were fertile. However, on closer examination, these mice displayed a wide variety of abnormalities. Collagen fiber patterns in skin were disordered, and abnormally large fibrils with irregular contours were observed by electron microscopy in both skin and tendon. As a functional correlate of these findings, the skin was fragile and had reduced tensile strength, and the tail was unusually flexible. Mutant skin fibroblasts were defective in attachment to a substratum. An increase in total density and in cortical thickness of long bones was documented by histology and quantitative computer tomography. Mutant mice also manifested an abnormal bleeding time, and histologic surveys of mouse tissues, stained with an antibody to von Willebrand factor, showed a significant increase in blood vessels. The basis for the unusual phenotype of the TSP2-null mouse could derive from the structural role that TSP2 might play in collagen fibrillogenesis in skin and tendon. However, it seems likely that some of the diverse manifestations of this genetic disorder result from the ability of TSP2 to modulate the cell surface properties of mesenchymal cells, and thus, to affect cell functions such as adhesion and migration.

1998

2/AB/25 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10797407 BIOSIS NO.: 199799418552
Identification of cell adhesive active sites in the N-terminal domain of thrombospondin-1.
AUTHOR: Clezardin Philippe(a); Lawler Jack; Amiral Jean; Quentin Gerard; Delmas Pierre
AUTHOR ADDRESS: (a)INSERM Research Unit 403, Pavillon F, Hopital Edouard Herriot, 69437 Lyon Cedex 03**France
JOURNAL: Biochemical Journal 321 (3):p819-827 1997
ISSN: 0264-6021
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Using a series of fusion proteins that span almost all of the thrombospondin-1 (TSP-1) molecule, we observed in this study that Chinese hamster ovary (CHO) K1 cells strongly attached to the N-terminus but not to the other domains of TSP-1 (e.g. the C-terminus, and type 1, type 2 and type 3 repeats). In addition, attachment to the N-terminus of CHO S745 cells defective in cellsurface glycosaminoglycans (GAGs) was decreased by 47% compared with that observed with CHO K1 cells, indicating the presence of GAG-dependent cell adhesive sites. With the aim of identifying these cell adhesive sites, a series of synthetic peptides, overlapping heparin-binding sequences ARKGSGRR (residues 22-29), MKKTRG (residues 79-84) and TRDLASIARLRIAKGVNDNF (residues

170-189), were synthesized and tested for their ability to support CHO cell attachment. Using both centrifugation and cell-attachment assays, MKKTRG-containing peptides promoted CHO K1 cell adhesion, while ARKGSGRR-containing peptides and peptide TRDLASIARLRIAKGVNDNF did not. CHO S745 cell attachment to MKKTRG-containing peptides was partially decreased. A 36% decrease in CHO K1 cell attachment to the N-terminus was also observed when the heparin-binding consensus sequence KKTR was mutated to QNTR. In addition, peptide MKKTRG partially inhibited (25% inhibition) CHO K1 cell attachment to the N-terminus. However, peptide MKKTRG was not sufficient to fully promote cell attachment to the N-terminus of TSP-1. Peptides VDAVRTEKGFLLLASLRQ and TLLALERKDHS also supported CHO K1 cell attachment in a GAG-dependent and -independent manner respectively. Moreover, CHO K1 cell attachment to MKKTRG was found to be markedly enhanced when flanked with the sequences VDAVRTEKGFLLLASLRQ and TLLALERKDHS. Peptide VDAVRTEKGFLLLASLRQMKKTRG nearly abolished (98% inhibition) CHO K1 cell attachment to the N-terminus, while peptides MKKTRG. MKKTRGTLLALERKDHS and VDAVRTEKGFLLLASLRQ had only a moderate inhibitory effect (25, 27 and 53% inhibition respectively). These data indicate that the sequence VDAVRTEKGFLLLASLRQMKKTRGTLLALERKDHS (residues 60-94) constitutes a GAG-dependent cell adhesive site in the N-terminus of TSP-1. Moreover, a GAG-independent site, encompassing residues 189-200 (FQGVLQNVRFVF), has been identified. These two adhesive sites supported the attachment of a wide variety of cells (human breast carcinoma , melanoma and osteosarcoma cells), and a high degree of sequence homology was found between TSP-1 and TSP -2 between residues 60 and 94 (48% identity) and 189-200 (67% identity), further suggesting the functional importance of these two cell adhesive sites in the N-terminus of TSP-1.

1997

2/AB/26 (Item 26 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10387183 BIOSIS NO.: 199699008328
Isolation of genes differentially expressed in human primary myoblasts and embryonal rhabdomyosarcoma.
AUTHOR: Genini Michele; Schwalbe Petra; Scholl Florence A; Schafer Beat W (a)
AUTHOR ADDRESS: (a)Dep. Pediatr., Div. Clinical Chem., Univ. Zurich, Steinwiesstrasse 75, Zurich**Switzerland
JOURNAL: International Journal of Cancer 66 (4):p571-577 1996
ISSN: 0020-7136
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Using a subtractive hybridization method, we have cloned 48 cDNAs which are expressed in human primary myoblasts but down-regulated in the embryonal-rhabdomyosarcoma (RMS) cell line RD. Twenty-nine sequences could be identified as coding for previously known gene products, while 19 encode unknown proteins. Twelve clones coding for known proteins that were highly down-regulated in the RD cells were chosen for further analysis on Northern blots containing additional normal and RMS cells. The expression pattern of TGF-beta-induced gene product-3 (beta-igH3), inhibitory G-protein alpha sub-unit (G-alpha-i2), osteoblast-specific factor-2 (OSF-2), 22-kDa smooth-muscle protein (SM22), clone A3351 (homologous to mouse talin), testican, thrombospondin-1 and thrombospondin -2 suggests involvement of these proteins in the genesis of the neoplastic phenotype. Among the clones with unknown sequence,

several are identical or homologous to expressed sequence tags or known cDNAs, such as integrins or laminin. These results suggest that several isolated clones might have an important role in the determination or maintenance of the normal phenotype, and thus their loss is possibly involved in the progression of malignancy .

1996

2/AB/27 (Item 27 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08969910 BIOSIS NO.: 199396121411
Differential expression of thrombospondin 1, 2, and 3 during murine development.
AUTHOR: Iruela-Arispe M Luisa; Liska Deann J; Sage E Helene; Bornstein Paul (a)
AUTHOR ADDRESS: (a)Dep. Biochem. SJ-70, Univ. Wash., Seattle, WA 98195**USA
JOURNAL: Developmental Dynamics 197 (1):p40-56 1993
ISSN: 1058-8388
DOCUMENT TYPE: Article; Erratum
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Thrombospondin 1 is a secreted, trimeric glycoprotein that mediates interactions between cells and extracellular matrix and exhibits cell-specific effects on migration and proliferation. Recently, two additional thrombospondin genes (thrombospondin 2 and 3) have been identified. To study the functions of these proteins, we have used in situ hybridization and RNAse protection assays to compare the expression of the genes encoding thrombospondin 1, 2, and 3 during murine embryogenesis. Thrombospondin mRNAs were associated with ossification, neuronal organogenesis, and lung development, although transcripts were differentially expressed. Thrombospondin 1 was predominant from days 10 to 13. During this period, high but transient levels of expression were observed in the neural tube, head mesenchyme, and cardiac cushions. In contrast, a more constant level of thrombospondin 1 mRNA was apparent in resident megakaryocytes of the liver, as well as in circulating megakaryocytes; neither thrombospondin 2 nor 3 was detected in these cells. Thrombospondin 1 was also produced by cells of the developing kidney and gut. The expression of thrombospondin 2 was confined principally to organized connective tissue that included pericardium, pleura, perichondrium, periosteum, meninges, ligaments, and reticular dermis . Thrombospondin 2 was also produced by differentiating skeletal myoblasts and by cells of the kidney and gut. Moreover, high levels of expression were detected in blood vessels. Thrombospondin 3 mRNA was restricted to brain, cartilage, and lung. Although thrombospondin 1, 2, and 3 belong to a family of structurally related genes, the differences observed in the spatiotemporal distribution of the corresponding mRNAs indicate unique functions for these secreted proteins.

1993

2/AB/28 (Item 28 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08852112 BIOSIS NO.: 199396003613
Thrombospondin is a tight-binding competitive inhibitor of neutrophil

elastase.
AUTHOR: Hogg Philip J(a); Owensby Dwain A; Mosher Deane F; Misenheimer Tina M; Chesterman Colin N
AUTHOR ADDRESS: (a)Dep. Haematol., Prince of Wales Hosp., High St., Randwick, NSW 2031**Australia
JOURNAL: Journal of Biological Chemistry 268 (10):p7139-7146 1993
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Thrombospondin, a glycoprotein of three identical disulfide-bonded subunits, is a constituent of platelet alpha-granules and a variety of normal and transformed cells and binds to cell surfaces and becomes incorporated into extracellular matrix. It has been implicated in processes such as wound healing and tumor growth and metastasis. In addition, thrombospondin was shown recently to be an inhibitor of the fibrinolytic enzyme, plasmin. In the cause of studying the effects of thrombospondin on other serine proteinases, we found that thrombospondin binds neutrophil elastase in an active-site-dependent manner and competitively inhibits the activity of the enzyme. In a competitive binding assay, neutrophil elastase bound to thrombospondin with a dissociation constant of 17 +- 7 nM, expressed per mole of thrombospondin trimer, or 52 +- 20 nM, expressed per mole of thrombospondin subunit. In kinetic studies of the inhibition of the amidolytic activity of neutrophil elastase by thrombospondin , 2 .7 +- 0.3 mol of elastase interacted with 1 mol of thrombospondin trimer with a site-binding constant of 57 +- 13 nM. Lower limits for the on rate constant of 5 times 10-6 M-1 s-1 and off rate constant of 0.27 s-1 were established. Affinity of binding of neutrophil elastase to thrombospondin was sensitive to ionic strength and calcium ions. Thrombospondin was cleaved by neutrophil elastase, but the site(s) of the limited cleavage are independent of the competitive inhibition of elastase activity by thrombospondin. Neutrophil elastase inactivated with phenylmethylsulfonyl fluoride did not compete with active elastase for binding to thrombospondin, implying that a functional active site is important for the interaction of elastase with thrombospondin. Thrombospondin protected fibronectin from cleavage by neutrophil elastase. In summary, the binding of neutrophil elastase to thrombospondin is tight, reversible, and close enough to the active site of elastase to exclude small synthetic tripeptidyl p-nitroanilide substrates and macromolecular protein substrates. Two potential reactive centers that may be involved in binding elastase have been identified in the calcium-binding type 3 domains of thrombospondin. Neutrophil elastase is the enzyme primarily responsible for degrading and solubilizing connective tissue during inflammatory processes. These findings suggest a previously unsuspected mechanism for regulation of elastase activity at inflammatory sites.

1993

2/AB/29 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09820698 Genuine Article#: 452RQ Number of References: 43
Title: Thrombospondin-1 and-2 messenger RNA expression in normal and neoplastic endometrial tissues: Correlation with angiogenesis and prognosis (ABSTRACT AVAILABLE)
Author(s): Seki N; Kodama J (REPRINT) ; Hashimoto I; Hongo A; Yoshinouchi M ; Kudo T
Corporate Source: Okayama Univ,Sch Med, Dept Obstet & Gynecol,2-5-1 Shikata

Cho/Okayama 7008558//Japan/ (REPRINT); Okayama Univ,Sch Med, Dept Obstet & Gynecol,Okayama 7008558//Japan/
Journal: INTERNATIONAL JOURNAL OF ONCOLOGY, 2001, V19, N2 (AUG), P305-310
ISSN: 1019-6439 Publication date: 20010800
Publisher: PROFESSOR D A SPANDIDOS, 1, S MERKOURI ST, EDITORIAL OFFICE,, ATHENS 116 35, GREECE
Language: English Document Type: ARTICLE
Abstract: The role of thrombospondin (TSP) in tumor angiogenesis and progression remains controversial. The expression of TSP-1 and TSP -2 mRNAs was assessed. Furthermore, TSP association with clinicopathological features, including microvessel count, regarding prognostic significance was examined. Expression of TSP-1 and TSP -2 were assessed by reverse transcriptase-polymerase chain reaction in 18 normal endometrium and 55 endometrial cancer samples. Microvessel counts were determined by immunostaining for factor VIII-related antigen in endometrial cancer specimens. TSP-1 expression of secretory phase endometrium was markedly higher than that of proliferative phase endometrium (p=0.047). Expression of TSP-1 and TSP -2 was detected in 33 (60.0%) and 15 cases (27.3%), respectively, of 55 endometrial cancer samples. TSP-1 expression was significantly higher in tumors recovered from elderly women (p=0.009). TSP -2 expression was significantly higher in malignancies exhibiting cervical and lymph-vascular space involvement (p=0.029 and p=0.009, respectively). Although not statistically significant, microvessel counts were higher in cases displaying increased TSP-1 expression. The microvessel count in patients with TSP -2 expression was markedly higher than that observed in patients lacking TSP -2 expression (p=0.026). Subjects demonstrating TSP -2 mRNA expression displayed significantly poorer prognosis than those lacking TSP -2 mRNA expression (p=0.016). There was no association between TSP-1 mRNA expression and patient outcome. Our findings provide evidence that elevated TSP expression may be associated with an angiogenic phenotype in endometrial cancer . In addition, TSP -2 expression is a marker for poor prognosis in this disease.

2/AB/30 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09305989 Genuine Article#: 390BX Number of References: 48
Title: Thrombospondin-1 and-2 in node-negative breast cancer: Correlation with angiogenic factors, p53, cathepsin D, hormone receptors and prognosis (ABSTRACT AVAILABLE)
Author(s): Gasparini G (REPRINT) ; Toi M; Biganzoli E; Dittadi R; Fanelli M ; Morabito A; Boracchi P; Gion M
Corporate Source: Azienda Complesso Osped San Filippo Neri,Div Med Oncol,Via Martinotti 20/I-00135 Rome//Italy/ (REPRINT); Azienda Complesso Osped San Filippo Neri,Div Med Oncol,I-00135 Rome//Italy/; Metropolitan Hosp,Dept Surg,Tokyo//Japan/; Ist Nazl Studio & Cura Tumori,Dept Med Stat & Biometry,I-20133 Milan//Italy/; Ctr Study Biol Markers Malignancy,Venice//Italy/; Univ Milan,Inst Med Stat & Biometry,Milan//Italy/
Journal: ONCOLOGY, 2001, V60, N1, P72-80
ISSN: 0030-2414 Publication date: 20010000
Publisher: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND
Language: English Document Type: ARTICLE
Abstract: Objective: Thrombospondins (TSPs) are a multigene family of five secreted glycoproteins involved in the regulation of cell proliferation, adhesion and migration. Two members of the TSP family, namely TSP-1 and TSP -2 , are also naturally occurring inhibitors of angiogenesis. The aim of the present study was to determine the

prognostic significance of the determination of TSP-1 and -2 and their correlation with the angiogenic peptides vascular endothelial growth factor (VEGF) and thymidine phosphorylase (TP), as well as with other biological and clinicopathological features investigated. Methods: We evaluated a series of 168 women with node-negative breast cancer with a median follow-up period of 66 months, not treated with adjuvant therapy. The cytosolic levels of TSP-1 and -2 were determined in the primary tumour by a commercially available immunometric assay. Results: We found that 166 tested tumours had measurable levels of TSP-1 and -2 protein (median value 5.978, range 0.579-31.410 ng/mg of protein). On the basis of Spearman's rank correlation coefficient, a weak inverse association of TSP-1 and -2 with tumour size and cathepsin D was found. Moreover, principal component analysis on ranks evidenced a poor association between TSP-1 and -2, VEGF and TP. The results of the clinical outcome were ana lysed by both univariate and multivarlate [for relapse-free survival (RFS) only]) Cox regression models. TSP-1 and -2 were not significant prognostic factors in univariate analysis for either RFS ($p = 0.427$) or overall survival ($p = 0.069$). To investigate the 'angiogenic balance hypothesis', bivariate analyses were performed to investigate the interactions of TSP-1 and -2 with VEGF, TP or p53, but none were included in the selected models. Finally, in multivariate analysis for RFS a baseline model, previously defined in a larger case series and inclusive of VEGF, TP and their interaction was adopted. It was highly significant ($p = 0.002$, Harrell c statistic value of 0.703); but when TSP-1 and -2 were added, their contribution was negligible ($p = 0.731$, Harrell c statistic value of 0.705). Conclusions: The results of this study suggest that TSP-1 and -2 do not provide additional prognostic contribution to the joint effects of VEGF and TP. In the series of node-negative breast cancer patients investigated, determination of the angiogenic peptides VEGF and TP gave significant prognostic information. On the contrary, TSP-1 and -2, potential naturally occurring negative regulators of angiogenesis, lacked of prognostic value.

2/AB/31 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09260298 Genuine Article#: 384PJ Number of References: 28
Title: Thrombospondin 2 modulates collagen fibrillogenesis and angiogenesis (ABSTRACT AVAILABLE)
Author(s): Bornstein P (REPRINT) ; Kyriakides TR; Yang ZT; Armstrong LC; Birk DE
Corporate Source: Univ Washington,Dept Biochem,Box 357350/Seattle//WA/98195 (REPRINT); Univ Washington,Dept Biochem,Seattle//WA/98195; Jefferson Med Coll,Dept Pathol Anat & Cell Biol,Philadelphia//PA/
Journal: JOURNAL OF INVESTIGATIVE DERMATOLOGY SYMPOSIUM PROCEEDINGS, 2000 , V5, N1 (DEC), P61-66
ISSN: 1087-0024 Publication date: 20001200
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148 USA
Language: English Document Type: ARTICLE
Abstract: Thrombospondin 2 (TSP2)-null mice, generated by targeted disruption of the Thbs2 gene, display a complex phenotype that is characterized, in part, by a variety of connective tissue abnormalities and increased vascular density in skin and subcutaneous tissues. In this paper we summarize the evidence that TSP2 functions as a matricellular protein to influence cell function by modulating cell-matrix interactions, rather than acting as an integral component of the matrix. Thus, the structurally abnormal collagen fibrils detected in skin appear to be the consequence of the defective

adhesion demonstrated by dermal fibroblasts in culture that, in turn, result from increased matrix metalloproteinase 2 (MMP2, gelatinase A) production by these cells. Corroborating evidence for such a mode of action comes from transmission electron microscopic images of developing flexor muscle tendons that show distinct abnormalities in fibroblast-collagen fibril interactions in TSP2-null tissue. The increased vascular density seen in skin of TSP2-null mice can be reproduced in a number of models of injury, including subcutaneous implantation of polyvinyl alcohol sponges and silicone rubber discs, and excisional skin wounds. Experiments are proposed to distinguish between a primarily endothelial cell versus an extracellular matrix origin for the increased angiogenesis in TSP2-null mice.

2/AB/32 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09260292 Genuine Article#: 384PJ Number of References: 56
Title: Tumor angiogenesis (ABSTRACT AVAILABLE)
Author(s): Detmar M (REPRINT)
Corporate Source: Massachusetts Gen Hosp,Dept Dermatol, CBRC,Bldg 149,13th St/Charlestown//MA/02129 (REPRINT); Massachusetts Gen Hosp,Dept Dermatol, CBRC,Charlestown//MA/02129; Harvard Univ,Sch Med,Charlestown//MA/
Journal: JOURNAL OF INVESTIGATIVE DERMATOLOGY SYMPOSIUM PROCEEDINGS, 2000 , V5, N1 (DEC), P20-23
ISSN: 1087-0024 Publication date: 20001200
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148 USA
Language: English Document Type: ARTICLE
Abstract: In order to grow beyond minimal size and to metastasize, tumors need to induce the growth of new blood vessels (angiogenesis). Whereas in normal tissues, vascular quiescence is maintained by the dominant influence of endogenous angiogenesis inhibitors over angiogenic stimuli, tumor angiogenesis is induced by increased secretion of angiogenic factors and/or by downregulation of angiogenesis inhibitors. Recent evidence suggests vascular endothelial growth factor (VEGF) as the major tumor angiogenesis factor, promoting tumor growth, invasion, and metastasis. Conversely, blocking of VEGF function inhibits angiogenesis and suppresses tumor growth in vivo. Newly identified members of the VEGF family of angiogenesis factors include placental growth factor, VEGF-B, VEGF-C, and VEGF-D, and show overlapping binding patterns to specific endothelial cell receptors. VEGF-C appears to play a major role as a lymphangiogenesis factor and as a growth factor for Kaposi's sarcoma, In contrast, endogenous inhibitors prevent blood vessel growth in normal tissues. In particular, thrombospondin-1 (TSP-1) and TSP -2 are expressed in normal skin and, when introduced into squamous cell carcinomas , potently inhibit malignant tumor growth via inhibition of tumor angiogenesis.

2/AB/33 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09106680 Genuine Article#: 367PJ Number of References: 43
Title: Angiogenesis modulators expression in culture cell lines positives for HPV-16 oncoproteins (ABSTRACT AVAILABLE)
Author(s): BequetRomero M (REPRINT) ; LopezOcejo O
Corporate Source: CTR GENET ENGN & BIOTECHNOL,DIV PHARMACEUT, POB 6162/HAVANA 10600//CUBA/ (REPRINT); CTR GENET ENGN & BIOTECHNOL,VACCINES DIV/HAVANA 10600//CUBA/

Journal: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, 2000, V277, N1 (OCT 14), P55-61
ISSN: 0006-291X Publication date: 20001014
Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
Language: English Document Type: ARTICLE
Abstract: Altered angiogenesis response is observed in patients with cervical cancer. In this study we examined whether Human Papilloma Virus (HPV) positive epithelial cells are able to produce angiogenic modulators. When added to human umbilical vein endothelial cells (HUVEC) the media conditioned by HPV-16 positive cells was able to induce proliferation, whereas a contrary effect was observed for media derived from non-tumorigenic keratinocytes. The analyses of angiogenesis modulator's mRNA levels result in a decrease of the antiangiogenic factors TSP-1 and 2 in HPV-16 positive cells. In contrast the expression of the proangiogenic molecules: bFGF, IL-8, TGF-beta, TNF alpha, and VEGF were higher in these cells as compared to control keratinocytes. Furthermore the pattern of VEGF isoforms observed in the cells positive for the viral genome point to a preferential induction of the VEGF(189) isoform. We therefore conclude that cervical cancer cells expressing HPV-16 genome are able to contribute to the pro-angiogenic response that might support tumor growth and invasion of the surrounding tissues. (C) 2000 Academic Press.

2/AB/34 (Item 6 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09085694 Genuine Article#: 366EB Number of References: 55
Title: Correlation of thrombospondin-1 and transforming growth factor-beta expression with malignancy of glioma (ABSTRACT AVAILABLE)
Author(s): Kawataki T; Naganuma H; Sasaki A; Yoshikawa H; Tasaka K; Nukui H
Corporate Source: YAMANASHI MED UNIV,DEPT NEUROSURG/TAMAHO/YAMANASHI 4093898/JAPAN/; YAMANASHI MED UNIV,DEPT PARASITOL & IMMUNOL/TAMAHO/YAMANASHI 4093898/JAPAN/
Journal: NEUROPATHOLOGY, 2000, V20, N3 (SEP), P161-169
ISSN: 0919-6544 Publication date: 20000900
Publisher: BLACKWELL SCIENCE ASIA, 54 UNIVERSITY ST, P O BOX 378, CARLTON VICTORIA 3053, AUSTRALIA
Language: English Document Type: ARTICLE
Abstract: The expression of thrombospondin-1 (TSP-1) and its role in gliomas have not been well examined. In the present study TSP-1 expression in a panel of malignant glioma cell lines and the expression of TSP-1 and transforming growth factor (TGF-beta) proteins in low-grade and malignant glioma tissues were investigated. Reverse transcription-polymerase chain reaction analysis showed that nine of nine malignant glioma cell lines expressed TSP-1 mRNA, and seven of nine glioma lines expressed TSP -2 mRNA. Production and secretion of TSP-1 were examined in the T98G glioblastoma cell line by western blot analysis. Total TSP-1 protein content in the supernatant was 10 times higher than that in the cell lysate. Secretion of TSP-1 was examined in these glioma cell lines by western blot analysis. All glioma lines secreted significant levels of TSP-1. Bioassay showed that all tumor lines had the capacity to activate latent TGF-beta. Localization of TSP-1, TGF-beta1, -beta2, and -beta3 was examined immunohistochemically in surgically resected glioma tissues, including 11 glioblastomas, six anaplastic astrocytomas, and eight astrocytomas. Most glioblastomas expressed high levels of both TSP-1 and TGF-beta. Anaplastic astrocytomas expressed moderate levels of TSP-1 and TGF-beta. Most malignant gliomas expressed various levels of TGF-beta1, -beta2, and -beta3. The expression of both proteins, however, was weak in low-grade

gliomas. Normal brain tissues around the tumors were negatively or very weakly positively stained for TSP-1 and TGF-beta. These results indicate that most malignant glioma cells express TSP-1 in vitro and in vivo, and the expression of TSP-1 and TGF-beta in vivo correlates with the histologic malignancy of glioma. Overexpression of both TSP-1 and TGF-beta may increase the biologic malignancy of malignant gliomas, through generating the active form of TGF-beta in tumor tissues.

2/AB/35 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08999033 Genuine Article#: 355BE Number of References: 19
Title: The physical properties of leathers made from the skins of mice genetically deficient in decorin or thrombospondin-2 (ABSTRACT AVAILABLE)
Author(s): Mozersky SM (REPRINT) ; Iandola SK; Liu CK; Phillips JG; Marmer WN; Eichstetter I; Iozzo RV
Corporate Source: USDA ARS,EASTERN REG RES CTR, 600 E MERMAID LANE/WYNDMOOR//PA/19038 (REPRINT); THOMAS JEFFERSON UNIV,DEPT PATHOL ANAT & CELL BIOL/PHILADELPHIA//PA/19107; THOMAS JEFFERSON UNIV,KIMMEL CANC CTR/PHILADELPHIA//PA/19107
Journal: JOURNAL OF THE AMERICAN LEATHER CHEMISTS ASSOCIATION, 2000, V95, N7 (SEP), P229-235
ISSN: 0002-9726 Publication date: 20000900
Publisher: AMER LEATHER CHEMISTS ASSN, ROOM 5 CAMPUS STATION-14 TANNER RES LAB, CINCINNATI, OH 45221
Language: English Document Type: ARTICLE
Abstract: The physical properties of leathers made from the skins of mice genetically deficient in decorin or thrombospondin -2 were compared to leathers made from the skins of control (normal) mice. Decorin deficiency was associated with a leather of significantly reduced tensile strength and stiffness. There was no evidence of a similar effect of thrombospondin -2 deficiency. Neither deficiency had a significant effect on the extensibility of the skin or of leather produced from it. The implications of these findings are discussed.

2/AB/36 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07621192 Genuine Article#: 182JL Number of References: 0
Title: The endogenous angiogenesis inhibitor thrombospondin- 2 is expressed in basal keratinocyte of normal epidermis in vivo and in epidermal keratinocytes in vivo
Author(s): Riccardi L; Streit M; Velasco P; Brown L; Lawler J; Detmar M
Corporate Source: BETH ISRAEL DEACONESS MED CTR,/BOSTON//MA/; HARVARD UNIV,SCH MED/BOSTON//MA/; MASSACHUSETTS GEN HOSP,DEPT DERMATOL, CUTANEOUS BIOL RES CTR/BOSTON//MA/02114
Journal: JOURNAL OF INVESTIGATIVE DERMATOLOGY, 1999, V112, N4 (APR), P 227-227
ISSN: 0022-202X Publication date: 19990400
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148
Language: English Document Type: MEETING ABSTRACT

2/AB/37 (Item 9 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07607181 Genuine Article#: 187BP Number of References: 37
Title: Mice that lack the angiogenesis inhibitor, thrombospondin 2, mount an altered foreign body reaction characterized by increased vascularity (ABSTRACT AVAILABLE)
Author(s): Kyriakides TR; Leach KJ; Hoffman AS; Ratner BD; Bornstein P (REPRINT)
Corporate Source: UNIV WASHINGTON,DEPT BIOCHEM, BOX 357350/SEATTLE//WA/98195 (REPRINT); UNIV WASHINGTON,DEPT BIOCHEM/SEATTLE//WA/98195; UNIV WASHINGTON,DEPT BIOENGN/SEATTLE//WA/98195; UNIV WASHINGTON,DEPT CHEM ENGN/SEATTLE//WA/98195
Journal: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, 1999, V96, N8 (APR 13), P4449-4454
ISSN: 0027-8424 Publication date: 19990413
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418
Language: English Document Type: ARTICLE
Abstract: Disruption of the thrombospondin 2 gene (Thbs2) in mice results in a complex phenotype characterized chiefly by abnormalities in fibroblasts, connective tissues, and blood vessels. Consideration of this phenotype suggested to us that the foreign body reaction (FBR) might be altered in thrombospondin 2 (TSP2)-null mice. To investigate the participation of TSP2 in the FBR, polydimethylsiloxane (PDMS) and oxidized PDMS (ox-PDMS) disks were implanted in TSP2-null and control mice. Growth of TSP2-null and control skin fibroblasts in vitro also was evaluated on both types of disks. Normal fibroblasts grew as a monolayer on both surfaces, but attachment of the cells to ox-PDMS was weak and sensitive to movement. TSP2-null fibroblasts grew as aggregates on both surfaces, and their attachment was further compromised on ox-PDMS. After a 4-week implantation period, both types of PDMS elicited a similar FBR with a collagenous capsule in both TSP2-null and control mice, However, strikingly, the collagenous capsule that formed in TSP2-null mice was highly vascularized and thicker than that formed in normal mice. In addition, abnormally shaped collagen fibers were observed in capsules from mutant mice. These observations indicate that the presence or absence of an extracellular matrix component, TSP2, can influence the nature of the FBR, in particular its vascularity. The expression of TSP2 therefore could represent a molecular target for local inhibitory measures when vascularization of the tissue surrounding an implanted device is desired.

2/AB/38 (Item 10 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07372495 Genuine Article#: 157AX Number of References: 28
Title: Thrombospondins I and II messenger RNA expression in lung carcinoma: Relationship with p53 alterations, angiogenic growth factors, and vascular density (ABSTRACT AVAILABLE)
Author(s): Fontanini G (REPRINT) ; Boldrini L; Calcinai A; Chine S; Lucchi M; Mussi A; Angeletti CA; Basolo F; Bevilacqua G
Corporate Source: UNIV PISA,DEPT ONCOL, DIV PATHOL, VIA ROMA 57/I-56126 PISA//ITALY/ (REPRINT); UNIV PISA,DEPT SURG, CHAIR THORAC SURG/I-56126 PISA//ITALY/
Journal: CLINICAL CANCER RESEARCH, 1999, V5, N1 (JAN), P155-161
ISSN: 1078-0432 Publication date: 19990100
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202
Language: English Document Type: ARTICLE
Abstract: Thrombospondin (TSP) is a M-r 450,000 multifunctional matrix

glycoprotein that interferes with tumor growth, angiogenesis, and metastasis, It has recently been shown that TSP expression is enhanced by the product of the p53 gene and that a down-regulation of TSP may be observed when alterations of the p53 protein occur. Moreover, a number of studies have demonstrated a regulatory activity of p53 on human vascular endothelial growth factor (VEGF), although additional investigations mill be necessary to understand their relationship. In non-small cell lung carcinoma (NSCLC), neoangiogenesis, p53 alterations, and VEGF expression seem to have meaningful implications in the development and progression of this type of cancer . The aim of this study is to identify and quantitate TSP I and TSP II mRNA in NSCLCs with respect to p53 alterations, angiogenic growth factor expression, and microvascular density. A series of 24 cases of NSCLC were analyzed. Eleven of 24 of the cases were positive for TSP II mRNA, whereas 8 of 24 showed TSP I mRNA expression. A significant inverse association was found between TSP I mRNA and fibroblast growth factor (FGF) protein expression (P = 0.00001), Tumors with low FGF protein expression (less than or equal to 40% of positive cells) presented a number of TSP I cDNA molecules, significantly higher than tumors expressing high levels of FGF protein. No association was found between TSP mRNA expression and other angiogenic growth factors (i.e., VEGF) or tumoral neovascularization. On the contrary, tumors with high levels of FGF showed a higher number of microvessels (P = 0.05), By PCR-single-strand conformational polymorphism analysis, we observed aberrations of the p53 gene in 19 of the 24 tumor samples. No association was found between p53 alterations and TSP mRNA expression, Instead, an interestingly significant association was found between the presence of p53 mutations and high VEGF protein expression (P = 0.01) and neovascularization (P = 0.03), Highly vascularized tumors showed higher VEGF protein expression (r = 0.45; P = 0.02), These data support the concept that in NSCLC, p53 exerts an important role in the control of neoangiogenesis. This influence is probably mediated by VEGF, The inverse association we found between TSP I and basic FGF suggests a different role of TSP I and TSP II in the angiogenic ''switch,'' supporting the hypothesis that especially TSP I may have a significant function in tumor angiogenesis.

2/AB/39 (Item 11 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06869269 Genuine Article#: ZY111 Number of References: 23
Title: Thrombospondin 2 gene expression is correlated with decreased vascularity in non-small cell lung cancer (ABSTRACT AVAILABLE)
Author(s): Oshika Y; Masuda K; Tokunaga T; Hatanaka H; Kamiya T; Abe Y; Ozeki Y; Kijima H; Yamazaki H; Tamaoki N; Ueyama Y; Nakamura M (REPRINT)
Corporate Source: TOKAI UNIV,SCH MED, DEPT PATHOL/KANAGAWA 2591193//JAPAN/ (REPRINT); TOKAI UNIV,SCH MED, DEPT PATHOL/KANAGAWA 2591193//JAPAN/; NATL DEF MED COLL,DEPT SURG 2/TOKOROZAWA/SAITAMA 3598513/JAPAN/
Journal: CLINICAL CANCER RESEARCH, 1998, V4, N7 (JUL), P1785-1788
ISSN: 1078-0432 Publication date: 19980700
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202
Language: English Document Type: ARTICLE
Abstract: Stromal vascularity is thought to be a major factor involved in the progression of carcinoma. However, the crucial mechanisms of vascularization in the stroma are not well understood, Vascularity could be regulated by various cytokines produced by neoplastic or stromal cells in carcinoma. Thrombospondin (TSP) has an inhibitory role against vascularization in vitro, although the biological significance of TSP has not been characterized in vivo, We examined expression of

TSP1 and TSP2 genes in 78 non-small cell lung cancers (NSCLCs) and 33 extraneoplastic lung tissue samples by reverse transcription-PCR, TSP1 expression was detected in 66.7% (52 of 78) of NSCLCs and in 69.7% (23 of 33) of extraneoplastic lung tissue specimens. TSP2 expression was seen in 48.7% (38 of 78) of NSCLCs, whereas 72.7% (24 of 33) of extraneoplastic lung tissue samples showed TSP2 gene expression. TSP2 expression was significantly decreased in NSCLC as compared with extraneoplastic lung tissue (chi(2) test, P = 0.019), Vascularity in the NSCLC was inversely correlated with TSP2 gene expression (Mann-Whitney U test, P = 0.009). Patients with adenocarcinoma positive for TSP2 gene expression (22 of 49) showed significantly better prognosis than those without TSP2 (27 of 49; Cox-Mantel test, P = 0.034). TSP1 expression showed no apparent correlation with these factors. These results suggested that TSP2 had an inhibitory role against vascularization and progression of NSCLC.

2/AB/40 (Item 12 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02684095 Genuine Article#: LW492 Number of References: 71
Title: DIFFERENTIAL EXPRESSION OF THROMBOSPONDIN-1, THROMBOSPONDIN-2, AND THROMBOSPONDIN-3 DURING MURINE DEVELOPMENT (Abstract Available)
Author(s): IRUELAARISPE ML; LISKA DJ; SAGE EH; BORNSTEIN P
Corporate Source: UNIV WASHINGTON,DEPT BIOCHEM SJ-70/SEATTLE//WA/98195; UNIV WASHINGTON,DEPT BIOCHEM SJ-70/SEATTLE//WA/98195; UNIV WASHINGTON,DEPT BIOL STRUCT/SEATTLE//WA/98195; UNIV WASHINGTON,DEPT MED/SEATTLE//WA/98195
Journal: DEVELOPMENTAL DYNAMICS; 1993, V197, N1 (MAY), P40-56
ISSN: 1058-8388
Language: ENGLISH Document Type: ARTICLE
Abstract: Thrombospondin 1 is a secreted, trimeric glycoprotein that mediates interactions between cells and extracellular matrix and exhibits cell-specific effects on migration and proliferation. Recently, two additional thrombospondin genes (thrombospondin 2 and 3) have been identified. To study the functions of these proteins, we have used in situ hybridization and RNAse protection assays to compare the expression of the genes encoding thrombospondin 1, 2, and 3 during murine embryogenesis. Thrombospondin mRNAs were associated with ossification, neuronal organogenesis, and lung development, although transcripts were differentially expressed. Thrombospondin 1 was predominant from days 10 to 13. During this period, high but transient levels of expression were observed in the neural tube, head mesenchyme, and cardiac cushions. In contrast, a more constant level of thrombospondin 1 mRNA was apparent in resident megakaryocytes of the liver, as well as in circulating megakaryocytes; neither thrombospondin 2 nor 3 was detected in these cells. Thrombospondin 1 was also produced by cells of the developing kidney and gut. The expression of thrombospondin 2 was confined principally to organized connective tissue that included pericardium, pleura, perichondrium, periosteum, meninges, ligaments, and reticular dermis . Thrombospondin 2 was also produced by differentiating skeletal myoblasts and by cells of the kidney and gut. Moreover, high levels of expression were detected in blood vessels. Thrombospondin 3 mRNA was restricted to brain, cartilage, and lung. Although thrombospondin 1, 2, and 3 belong to a family of structurally related genes, the differences observed in the spatiotemporal distribution of the corresponding mRNAs indicate unique functions for these secreted proteins. (C) 1993 Wiley-Liss, Inc.

2/AB/41 (Item 1 from file: 35)
DIALOG(R)File 35:Dissertation Abs Online

01473787 AADAAI9609695
THE CDNA SEQUENCE, CHROMOSOMAL LOCATION AND CHARACTERIZATION OF TWO NOVEL CDNAS IN HUMANS: THROMBOSPONDIN 2 AND DERMAL FIBROBLAST HEPARAN SULFATE N-DEACETYLASE/N-SULFOTRANSFERASE

Author: LABELL, TERRY LEE
Degree: PH.D.
Year: 1995
Corporate Source/Institution: UNIVERSITY OF WASHINGTON (0250)
Source: VOLUME 56/12-B OF DISSERTATION ABSTRACTS INTERNATIONAL.
PAGE 6559. 98 PAGES

The processes of cell adhesion, locomotion, differentiation and development involve interactions between cell surfaces and extracellular matrix components. To understand the role of the extracellular matrix in these processes, one must first identify the proteins involved. Toward this end, the cDNAs for two new proteins, human thrombospondin 2 (hTSP2), an extracellular matrix glycoprotein, and human fibroblast heparan sulfate N-deacetylase/N-sulfotransferase (ND/NS), a golgi resident heparan sulfate modifying enzyme, were identified and cloned.

Thrombospondin 2 encodes a 1172 amino acid protein, which conserves the domains and repeats identified in thrombospondin 1. TSP2 exhibits a gradient of homology with thrombospondin 1 and contains binding sequences for heparin and heparan sulfate proteoglycans, CD36, the $\alpha\rm\sb{v}\beta\sb3$ class of integrins and a recently identified 80,000/105,000 Da receptor. A motif common to members of the cytokine receptor family and a motif common to a group of serum and/or growth factor inducible proteins are also present. The $3\sp\prime$ untranslated region contains sequences implicated in the regulation of mRNA stability and an 89-bp segment, 92% identical to the same region of the thrombospondin 2 mouse homologue. TSP2 hybridizes to a 7.5-kb message by Northern analysis and its gene is located at 6q27 in the human genome. The gene is transcribed in fibroblasts, smooth muscle cells and an osteosarcoma cell line, but its transcript is absent from umbilical vein endothelial cells and platelets under our study conditions. The identification of human thrombospondin 2 established the existence of a thrombospondin gene family in humans which now includes four members.

The 3563-bp human fibroblast heparan sulfate N-deacetylase/N-sulfotransferase cDNA encodes a 882 amino acid protein, but the reported $5\sp\prime$ and $3\sp\prime$ untranslated regions are not complete. The ND/NS cDNA hybridizes to a 8.5-kb and 4.2-kb transcript by Northern analysis and the gene is located at 5q33 in the human genome. The mouse homologue is located at a syntenic region of mouse chromosome 18, region E1. In situ hybridization experiments reveal that the ND/NS transcript is expressed in most tissues throughout mouse embryo development with particularly intense expression during odontogenesis of 1st and 2nd molars at day 16.5 p.c.

2/AB/42 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

14964442 PASCAL No.: 01-0117423
Comparative study of angiostatic and anti-invasive gene expressions as prognostic factors in gastric cancer

JI HEE LEE; JEONG TAE KOH; BOO AHN SHIN; KYU YOUN AHN; JUNG HO ROH; YOUNG JIN KIM; KYUNG KEUN KIM
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Journal: International journal of oncology, 2001, 18 (2) 355-361
Language: English

Genes involving angiogenesis and metastasis play an important role in the progression and infiltration of cancer . We examined the expressions of various angiostatic and potential invasion/metastasis suppressor genes through RT-PCR analyses in 32 gastric cancer specimens with or without distant metastasis. The expressions of the invasion/ metastasis suppressor, nm23 and E-cadherin increased much more in the cancer tissue (CT) and metastatic lymph node (MLN) than in the extraneoplastic mucosa (EM) and non-metastatic lymph node (NLN), respectively. The expressions of the angiostatic factor, angiopoietin 2 and thrombospondin 2 increased in the CT and MLN as compared with the EM and NLN, respectively. The newly cloned angiostatic factor, brain-specific angiogenesis inhibitor 1 (BAI1) decreased much more in the CT and MLN than the EM and NLN, respectively. However, BAI1 increased in the CT compared with the EM among the patients with poor prognosis and distant metastasis, such as liver or peritoneum. The expressions of the invasive factor, matrix metalloproteinase-2 and its suppressor, tissue inhibitor metalloproteinase-2 (TIMP-2) increased in the CM as compared with the EM, but the increased expression pattern of these genes in the CT became blunted among the patients with good prognosis. Our results indicate that BAI1 and TIMP-2 expressions in the extraneoplastic mucosa and non-metastatic lymph nodes were not suppressed in the patients with good prognosis, but increased expressions of angiopoietin 2, thrombospondin 2 , TIMP-2, nm23 and E-cadherin in the tumor tissue did not lead to a long survival after operation. It is suggested that the extent of BAI1 and TIMP-2 expression in the gastric mucosa may be an important prognostic factor for predicting survival in gastric cancer .

2/AB/43 (Item 1 from file: 351)
DIALOG(R)File 351:Derwent WPI

013484188
WPI Acc No: 2000-656131/200063
XRAM Acc No: C00-198554
Treating a disorder characterized by unwanted cell proliferation e.g. precancerous, cancerous or neoplastic cells or presence of tumor preferably of skin or prostate, comprises increasing thrombospondin-2 activity
Patent Assignee: GEN HOSPITAL CORP (GEHO)
Inventor: DETMAR M; STREIT M
Number of Countries: 092 Number of Patents: 002
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200057899	A1	20001005	WO 2000US7835	A	20000324	200063	B
AU 200039172	A	20001016	AU 200039172	A	20000324	200106	

Priority Applications (No Type Date): US 99127221 A 19990331
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200057899	A1	E	73	A61K-038/16	

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

AU 200039172 A A61K-038/16 Based on patent WO 200057899

Abstract (Basic): WO 200057899 A1
Abstract (Basic):

NOVELTY - Treating (M1) a subject having a disorder characterized by unwanted cell proliferation, comprising increasing thrombospondin-2 (TSP-2) activity, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) treating (M2) an unwanted skin condition comprising modulating TSP -2 activity;

(2) diagnosing (M3) a subject at risk of unwanted cell proliferation comprising evaluating the presence of TSP-2 nucleic acid or its protein; and

(3) identifying (M4) a compound which can be used to treat a disorder characterized by unwanted cell proliferation comprising treating a cell, tissue or subject with a candidate compound, and determining the level of TSP-2 nucleic acid or its protein, where the ability of the compound to increase TSP-2 nucleic acid or its protein, indicates that the compound is useful for treating the disorder.

ACTIVITY - Cytostatic; antiinflammatory; antipsoriatic.

MECHANISM OF ACTION - TSP-2 agonist (claimed); gene therapy. No biological data is given.

USE - To treat a subject having a disorder affecting epithelial tissue characterized by unwanted cell proliferation preferably precancerous, cancerous or neoplastic cells or the presence of tumors preferably of the skin, such as squamous cell carcinoma of the skin or a malignant melanoma, or of the prostate (claimed). The disorder is characterized by benign unwanted skin proliferation, such as psoriasis or papilloma formation (claimed). Evaluating the presence of TSP -2 nucleic acid or protein is useful for diagnosing the subject at risk for unwanted proliferation such as squamous cell carcinoma , melanoma or prostate cancer .

pp; 73 DwgNo 0/0

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